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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
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TITLE OF THE INVENTION (500 characters max)

PHARMACEUTICAL COMPOSITIONS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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☐ Application Data Sheet. See 37 CFR 1.76

☐ CD(s), Number

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METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

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Respectfully submitted,

SIGNATURE _____ Date 01/21/03

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TELEPHONE (781) 674-8000 Docket Number: T034.A/US

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This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

Docket No.: T034.A/US

Title: PHARMACEUTICAL COMPOSITIONS
By: Orn Almarsson and Julius F. Remenar
Filed: Herewith

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.10

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Cheryl Middleton

Date: January 21, 2003

Pharmaceutical Compositions

INCORPORATION BY REFERENCE

The content of US application No. 60/436,979, filed December 30, 2002 is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to drug-containing compositions, pharmaceutical compositions comprising such drugs, and methods for preparing same.

BACKGROUND OF THE INVENTION

Drugs in pharmaceutical compositions can be prepared in a variety of different forms. Such drugs can be prepared so as to have a variety of different chemical forms including chemical derivatives or salts. Such drugs can also be prepared to have different physical forms. For example, the drugs may be amorphous or may have different crystalline polymorphs, perhaps existing in different solvation or hydration states. By varying the form of a drug, it is possible to vary the physical properties thereof. For example, crystalline polymorphs typically have different solubilities from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapour pressure, density, colour, and compressibility. Accordingly, variation of the solvation state of a drug is one of many ways in which to modulate the physical properties thereof.

A solvate may be defined as a compound formed by solvation, for example as a combination of solvent molecules with molecules or ions of a solute. Well known solvent molecules include water, alcohols and other polar organic solvents. Alcohols include methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and t-butanol. Alcohols also include polymerized alcohols such as polyalkylene glycols (e.g., polyethylene glycol, polypropylene glycol). The best-known and preferred solvent is

typically water, and solvate compounds formed by solvation with water are termed hydrates.

Propylene glycol (1,2-propylene glycol) is a known substance which is a liquid at ambient temperature. As far as the applicants are aware, propylene glycol is not generally well-known for use in the formation of solvates. US3970651 does disclose the use of propylene glycol in the formation of a crystalline cephalosporin derivative. According to this disclosure a propylene glycolate derivative of a specific cephalosporin zwitterion may be formed in the presence of propylene glycol at acidic pH. This disclosure indicates that the propylene glycol derivative is more stable in solid form than the corresponding ethanolate, especially having excellent colour stability and thermal stability. No other solvates are disclosed in this US patent other than the specific solvate of cephalosporin.

In pharmaceutical formulations certain chemical classes of drugs pose particular problems in preparing pharmaceutical formulations for medical use. One such problem arises in the case of hygroscopic drugs, which tend to absorb water from the air. This is disadvantageous because it makes storage of the drug difficult and can cause degradation of the drug in some cases. Another problem in formulation arises with insoluble or sparingly soluble compounds for use as drugs. Such drugs having low aqueous solubility may need to be treated or derivatised so as to render them more soluble in water.

SUMMARY OF THE INVENTION

It has now been found that relatively stable forms of hygroscopic drugs can be prepared reliably and inexpensively. Moreover, insoluble or sparingly soluble drugs can have their aqueous solubility increased in a relatively simple way.

In a first aspect, the present invention provides a pharmaceutical composition comprising a propylene glycol solvate of a drug which is hygroscopic or has low aqueous solubility.

It has surprisingly been found that by using propylene glycol to form a solvate of a hygroscopic drug, the hygroscopicity of the drug is decreased and/or the aqueous solubility is increased. The drug is therefore much easier to formulate and store than its counterpart untreated or hydrated form.

A number of advantages arise from the use of propylene glycol in this way. First of all, a higher temperature is required to remove propylene glycol as compared with water or ethanol. This therefore results in an increased thermal stability. Secondly, propylene glycol solvates are generally more pharmaceutically acceptable than other common solvates, including those formed from alcohols other than ethanol. In addition, the solvates of the present invention have fewer solvation states than hydration states. This is beneficial because A particularly important aspect of the present invention is the realisation that formation of propylene glycol solvates is applicable in a general way to drugs whereby the above advantages may be conferred. The invention is particularly applicable to those drugs which are in the form of metal salts, such as alkali metal or alkaline earth metal salts. This is especially the case where the metal is selected from sodium, potassium, lithium, calcium and magnesium. Such salts can be hygroscopic and it has hitherto been difficult to find a suitable general means of formulation for these drugs.

Generally, the molar ratio of propylene glycol to drug in the solvate is in the range 0.5 to 2. Depending on the nature of the drug, the ratio of propylene glycol to drug in the solvate may be approximately 1 or approximately 2.

The composition may further comprise a pharmaceutically-acceptable diluent, excipient or carrier and details of pharmaceutical compositions are also set out in further detail below. The solvate of the pharmaceutical composition according to the present invention is preferably in a crystalline form.

Advantageously, the powder X-ray diffraction spectrum of the composition according to the invention differs from the corresponding powder X-ray diffraction spectrum of unsolvated drug by at least one property selected from:

(i) a loss of at least one peak;

(ii) shifting of more than half the peaks at the 2-theta angle by at least 0.3°; and

(iii) formation of at least one new peak.

It is preferred that the solvate is stable to temperatures of up to 50°C under a stream of gas in a thermogravimetric analysis apparatus.

In one aspect of the invention, the drug is a hygroscopic drug. A non-exhaustive list of hygroscopic drugs is set out in Table 1, along with their suppliers and routes of administration.

Table 1

Product (company)	**Active ingredient**	**Hygroscopic**	**Route(s) of Administration**
Solu-Medrol (P&U)	Methyl prednisolone succinate ester	X	IV
Primaxin IV and IM (Merck)	Imipenem/cilastatin	X (cilastatin)	IV/IM
Vitravene Injection (CIBA)	Fomivirsen sodium	X	IV
Baycol (Bayer)	Cerivastatin sodium	X	Oral
Synercid IV (Aventis)	Dalfopristin/Quinopristin	X	IV
Factrel (Wyeth)	Gonadorelin HCl (decapeptide)	X	IV/SC
Clindets Pledgets (Stiefel)	Clindamycin phosphate (ester prodrug)	X	Topical
Famvir (SKB)	Famciclovir	X	Oral
Nascobal Gel (Schwarz)	Cyanocobalamin	X	
Tasmar (Roche)	Tolcapone	X	Oral
Ellence Injection (P&U)	Epirubicin HCl	X	IV
Colestid (P&U)	Colestipol HCl (anion exc.)	X	Oral
Product (company)	**Active ingredient**	**Hygroscopic**	**Route(s) of Administration**
Pfizerpen Injection (Pfizer)	Penicillin G potassium	X	IV
Bacitracin Injection (Paddock)	Bacitracin (peptide)	X	IV
Lescol (Novartis)	Fluvastatin sodium	X	Oral
Voltaren XR (Novartis)	Diclofenac sodium	X	Oral
Salagen (MGI)	Pilocarpine HCl	X	Oral
Urecholine injection (Merck)	Bethanechol chloride	X	IV

Syprine (Merck)	Trientine 2(HCl)	X	Oral
Singulair chewable (Merck)	Montelukast sodium	X	Oral
Mustargen injection (Merck)	Mechlorethamine HCl	X	IV
Hydrocortone phosphate injection (Merck)	Hydrocortisone phosphate ester	X	IV
Decadron phosphate injection (Merck)	Dexamethasone phosphate ester	X	IV
Gastrocrom (Medeva)	Chromolyn sodium	X	Oral
Mestinon (ICN)	Pyridostigmine bromide	X	Oral
Adipex-P (Gate)	Phentermine HCl	X	Oral
Micardis (Boehringer-Ingelh.)	Telmisartan	X	Oral
Cerubidine injection (Bedford)	Daunorubicin HCl	X	IV
Biltricide (Bayer)	Praziquantel	X	Oral
Elmiron (Alza)	Pentosan polysulfate sodium	X	Oral

In one embodiment, the drug comprises celecoxib. Although the invention is not limited to this particular drug, celecoxib provides a suitable example of the efficacy of the invention. Further details of celecoxib are set out below. In a further embodiment, the drug comprises naproxen, further details of which are also set out below.

In another aspect of the invention, the drug has low aqueous solubility. For the purposes of the present application, a drug which has low aqueous solubility typically has a solubility of

An important class of drugs which have low aqueous solubility is the steroids. Particularly important steroids include . Formulating steroid drugs presents a problem because of their low aqueous solubility. It is difficult to make crystals of steroids because of their planar structure. Steroids generally tend to form channel hydrates in which water molecules are trapped in channels between planar steroid regions. Metal salts of steroid drugs can be made and are another example of hygroscopic drugs in accordance with one aspect of the present invention. Steroid drugs, whether hygroscopic or not, advantageously form solvates with propylene glycol, whereby the steroids are rendered acceptable for pharmaceutical use and are easier to handle than their corresponding hydrates.

In a further aspect, the present invention provides a method for preparing a propylene glycol solvate of a drug, which method comprises:

(a) contacting propylene glycol with a drug in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) collecting the solvate. The drug may be a hygroscopic drug or a drug of low aqueous solubility.

In a further aspect, the present invention provides a method for decreasing the hygroscopicity of a drug, which method comprises

(a) contacting the drug with propylene glycol in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) collecting the solvate, wherein the solvate has decreased hygroscopicity as compared to the drug.

In a further aspect, the present invention provides a method for increasing the aqueous solubility of a drug, which method comprises

(a) contacting the drug with propylene glycol in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) collecting the solvate, wherein the solvate has increased aqueous solubility as compared to the drug.

Typically, the step of crystallizing the solvate comprises changing the pH of the solution to precipitate the solvate. The pH may be raised to render the solution alkaline in order to achieve precipitation in the case of many drugs.

The step of collecting the solvate may include separating the solution phase from the solvate. Any common method of separation may be employed, including filtration and decanting. The crystalline solvate is preferably dried to remove excess solution phase. Drying may be carried out by thermal processing, vacuum, blowing a stream of gas such

as air, nitrogen, argon or another inert gas, or a combination of any or all of these methods.

The invention will now be described in further detail, by way of example only, with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a differential scanning calorimetry trace of the sodium salt of celecoxib prepared by Example 1 between 50°C and 110°C.

Fig. 2 shows a thermogravimetric analysis of the sodium salt of celecoxib prepared by Example 1, which was conducted from about 30°C to about 160°C.

Fig. 3 shows a powder x-ray diffraction plot of the sodium salt of celecoxib prepared by Example 1.

Fig. 4 shows a differential scanning calorimetry analysis of celecoxib lithium salt MO-116-49B.

Fig. 5 shows a thermogravimetric analysis of celecoxib lithium salt MO-116-49B.

Fig. 6 shows the RAMAN spectrum of celecoxib lithium salt MO-116-49B.

Fig. 7 shows the PXRD spectrum of celecoxib lithium salt MO-116-49B.

Fig. 8 shows a differential scanning calorimetry analysis of celecoxib potassium salt MO-116-49A.

Fig. 9 shows a thermogravimetric analysis of celecoxib potassium salt MO-116-49A.

Fig. 10 shows the RAMAN spectrum of celecoxib potassium salt MO-116-49A.

Fig. 11 shows the PXRD spectrum of celecoxib potassium salt MO-116-49A.

Fig. 12 shows a thermogravimetric analysis of a propylene glycol solvate of a celecoxib sodium salt.

Fig. 13 shows the PXRD spectrum of a propylene glycol solvate of a celecoxib sodium salt.

Fig. 14 shows a thermogravimetric analysis a propylene glycol solvate of a celecoxib potassium salt.

Fig. 15 shows the PXRD spectrum of a propylene glycol solvate of a celecoxib potassium salt.

Fig. 16 shows a thermogravimetric analysis of a propylene glycol solvate of a celecoxib lithium salt.

Fig. 17 shows the PXRD spectrum of a propylene glycol solvate of Naproxen sodium salt.

Fig. 18 shows a thermogravimetric analysis of a propylene glycol solvate of Naproxen sodium salt.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to propylene glycol solvate forms of certain drugs, including those which are hygroscopic or which have low aqueous solubility. Whilst the invention is applicable to any such drugs in general, metal salts of the non-steroidal antiinflammatory drug celecoxib serve to illustrate the present invention by way of example. Unlike traditional non-steroidal antiinflammatory drugs (NSAIDs), celecoxib is a selective inhibitor of cyclooxygenase II (COX-2) which causes fewer side effects when administered to a subject. The present applicants have identified new forms of celecoxib which have improved properties, particularly as oral formulations. The applicants have found that a stable, crystalline sodium salt of celecoxib can be synthesised which is significantly more soluble in water than the neutral celecoxib on the market. This sodium salt, or other metal salts can subsequently be improved according to the present invention by the production of a propylene glycol solvate thereof.

Due to the high pK_a of celecoxib (approximately 11), salts only form under strongly basic conditions. Typically, more than about one equivalent of a base is required to convert celecoxib to its salt form. A suitable aqueous solution for converting celecoxib to a salt has a pH of about 11.0 or greater, about 11.5 or greater, about 12 or greater, or about 13 or greater. Typically, the pH of such a solution is about 12 to about 13.

Salts of celecoxib are formed by reaction of celecoxib with an acceptable base. Acceptable bases include, but are not limited to, metal hydroxides and alkoxides. Metals include alkali metals (sodium, potassium, lithium, cesium), alkaline earth metals (magnesium, calcium), zinc, aluminum, and bismuth. Alkoxides include methoxide, ethoxide, n-propoxide, isopropoxide and t-butoxide. Additional bases include arginine, procaine, and other molecules having amino or guanidinium moieties with sufficiently high pK_a=s (e.g., pK_a=s greater than about 11, pK_a=s greater than about 11.5, or pK_a=s greater than about 12), along with compounds having a carbon-alkali metal bond (e.g., t-butyl lithium). Sodium hydroxide and sodium ethoxide are preferred bases. The amount of base used to form a salt is typically about one or more, about two or more, about three or more, about four or more, about five or more, or about ten or more equivalents relative to celecoxib. Preferably, about three to about five equivalents of one or more bases are reacted with celecoxib to form a salt.

A celecoxib salt can be transformed into a second celecoxib salt by transmetallation or another process that replaces the cation of the first celecoxib salt. In one example, a sodium salt of celecoxib is prepared and is subsequently reacted with a second salt such as an alkaline earth metal halide (e.g., $MgBr_2$, $MgCl_2$, $CaCl_2$, $CaBr_2$), an alkaline earth metal sulfate or nitrate (e.g., $Mg(NO_3)_2$, $Mg(SO_4)_2$, $Ca(NO_3)_2$, $Ca(SO_4)_2$), or an alkaline metal salt of an organic acid (e.g. calcium formate, magnesium formate, calcium acetate, magnesium acetate, calcium propionate, magnesium propionate) to form an alkaline earth metal salt of celecoxib.

The celecoxib salt can be characterized by differential scanning calorimetry (DSC). The sodium salt of celecoxib prepared in (Comparative) Example 1 is characterized by at least 3 overlapping endothermic transitions between 50°C and 110°C (Fig. 1). Conditions for DSC can be found in Example 1.

Celecoxib salts can be characterized by thermogravimetric analysis (TGA). The sodium salt of celecoxib prepared by Example 1 was characterized by TGA, and had about 3

loosely bound equivalents of water that evaporated between about 30°C and about 40°C, one more tightly bound equivalent of water that evaporated between about 40°C and about 100°C, and one very tightly bound equivalent of water that evaporated between about 140°C and about 160°C (Fig. 2). Conditions for TGA can be found in Example 1.

Celecoxib salts can also be characterized by powder x-ray diffraction (PXRD). The sodium salt of celecoxib prepared by Example 1 had an intense reflection or peak at a 2-theta angle of 6.40°, and other reflections or peaks at 7.01°, 16.73°, and 20.93° (Fig. 3). Conditions for PXRD can be found in Example 1.

Naproxen is a further drug which may be used to illustrate the present invention. Naproxen is a member of the ibufenac group of NSAIDs. This drug is practically insoluble in water.

Excipients employed in pharmaceutical compositions of the present invention can be solids, semi-solids, liquids or combinations thereof. Preferably, excipients are solids. Compositions of the invention containing excipients can be prepared by any known technique of pharmacy that comprises admixing an excipient with a drug or therapeutic agent. A pharmaceutical composition of the invention contains a desired amount of celecoxib per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a dispersion, a liquid, or any other form reasonably adapted for such administration. If intended for parenteral administration, it can be in the form, for example, of a suspension or transdermal patch. If intended for rectal administration, it can be in the form, for example, of a suppository. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the drug, such as tablets or capsules.

Non-limiting examples follow of excipients that can be used to prepare pharmaceutical compositions of the invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable carriers or diluents as excipients. Suitable carriers or diluents illustratively include, but are not limited to, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (e.g., Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of alpha- and amorphous cellulose (e.g., RexcelJ), powdered cellulose, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC); calcium carbonate; glycine; bentonite; block co-polymers; polyvinylpyrrolidone; and the like. Such carriers or diluents, if present, constitute in total about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 20% to about 80%, of the total weight of the composition. The carrier, carriers, diluent, or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose, mannitol, dibasic sodium phosphate, and microcrystalline cellulose (particularly Avicel PH microcrystalline cellulose such as Avicel PH 101), either individually or in combination, are preferred diluents. These diluents are chemically compatible with celecoxib. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a granulated composition) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides compositions having suitable release rates of celecoxib, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties and tablet properties.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet formulations. Suitable disintegrants include, but are not limited to, either individually or in combination, starches, including sodium starch glycolate (e.g., Explotab™ of PenWest) and pregelatinized corn starches (e.g., National™ 1551 of National Starch and Chemical Company, National™ 1550, and Colocorn™ 1500), clays (e.g., Veegum™ HV of R.T. Vanderbilt), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (e.g., Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to granulated pharmaceutical compositions of the present invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Such binding agents may also

prevent or inhibit crystallization or recrystallization of a celecoxib salt of the present invention once the salt has been dissolved in a solution. Suitable binding agents and adhesives include, but are not limited to, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (e.g., National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (e.g., Tylose™); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (e.g., Klucel™ of Aqualon); and ethylcellulose (e.g., Ethocel™ of the Dow Chemical Company). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the pharmaceutical composition.

Many of the binding agents are polymers comprising amide, ester, ether, alcohol or ketone groups and, as such, are preferably included in pharmaceutical compositions of the present invention. Polyvinylpyrrolidones such as povidone K-30 are especially preferred. Polymeric binding agents can have varying molecular weight, degrees of crosslinking, and grades of polymer. Polymeric binding agents can also be copolymers, such as block co-polymers that contain mixtures of ethylene oxide and propylene oxide units. Variation in these units' ratios in a given polymer affects properties and performance. Examples of block co-polymers with varying compositions of block units are Poloxamer 188 and Poloxamer 237 (BASF Corporation).

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the celecoxib in close association with water, a condition that is believed to improve bioavailability of the composition. Such wetting agents can also be useful in solubilizing or increasing the solubility of metal salts of celecoxib.

Non-limiting examples of surfactants that can be used as wetting agents in pharmaceutical compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (e.g., Labrasol™ of Gattefosse), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (e.g., Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (e.g., Lauroglycol™ of Gattefosse), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the pharmaceutical composition.

Wetting agents that are anionic surfactants are preferred. Sodium lauryl sulfate is a particularly preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about 4%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, but are not limited to, either individually or in combination, glyceryl behapate (e.g., Compritol™ 888 of Gattefosse); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated

vegetable oils (e.g., Sterotex™ of Abitec); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (e.g., Carbowax™ 4000 and Carbowax™ 6000 of the Dow Chemical Company); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0. 1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the pharmaceutical composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include, but are not limited to, talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, more preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include, but are not limited to, colloidal silicon dioxide, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal silicon dioxide is particularly preferred.

Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in pharmaceutical compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents.

Optionally, one or more effervescent agents can be used as disintegrants and/or to enhance organoleptic properties of pharmaceutical compositions of the invention. When

present in pharmaceutical compositions of the invention to promote dosage form disintegration, one or more effervescent agents are preferably present in a total amount of about 30% to about 75%, and preferably about 45% to about 70%, for example about 60%, by weight of the pharmaceutical composition.

According to a particularly preferred embodiment of the invention, an effervescent agent, present in a solid dosage form in an amount less than that effective to promote disintegration of the dosage form, provides improved dispersion of the celecoxib in an aqueous medium. Without being bound by theory, it is believed that the effervescent agent is effective to accelerate dispersion of the drug, such as celecoxib, from the dosage form in the gastrointestinal tract, thereby further enhancing absorption and rapid onset of therapeutic effect. When present in a pharmaceutical composition of the invention to promote intragastrointestinal dispersion but not to enhance disintegration, an effervescent agent is preferably present in an amount of about 1% to about 20%, more preferably about 2.5% to about 15%, and still more preferably about 5% to about 10%, by weight of the pharmaceutical composition.

An "effervescent agent" herein is an agent comprising one or more compounds which, acting together or individually, evolve a gas on contact with water. The gas evolved is generally oxygen or, most commonly, carbon dioxide. Preferred effervescent agents comprise an acid and a base that react in the presence of water to generate carbon dioxide gas. Preferably, the base comprises an alkali metal or alkaline earth metal carbonate or bicarbonate and the acid comprises an aliphatic carboxylic acid.

Non-limiting examples of suitable bases as components of effervescent agents useful in the invention include carbonate salts (e.g., calcium carbonate), bicarbonate salts (e.g., sodium bicarbonate), sesquicarbonate salts, and mixtures thereof. Calcium carbonate is a preferred base.

Non-limiting examples of suitable acids as components of effervescent agents and/or solid organic acids useful in the invention include citric acid, tartaric acid (as D-, L-, or

D/L-tartaric acid), malic acid, maleic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides of such acids, acid salts of such acids, and mixtures thereof. Citric acid is a preferred acid.

In a preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the weight ratio of the acid to the base is about 1:100 to about 100:1, more preferably about 1:50 to about 50:1, and still more preferably about 1:10 to about 10:1. In a further preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the ratio of the acid to the base is approximately stoichiometric.

Excipients which solubilize metal salts of drugs like celecoxib typically have both hydrophilic and hydrophobic regions, or are preferably amphiphilic or have amphiphilic regions. One type of amphiphilic or partially-amphiphilic excipient comprises an amphiphilic polymer or is an amphiphilic polymer. A specific amphiphilic polymer is a polyalkylene glycol, which is commonly comprised of ethylene glycol and/or propylene glycol subunits. Such polyalkylene glycols can be esterified at their termini by a carboxylic acid, ester, acid anhyride or other suitable moiety. Examples of such excipients include poloxamers (symmetric block copolymers of ethylene glycol and propylene glycol; e.g., poloxamer 237), polyalkyene glycolated esters of tocopherol (including esters formed from a di- or multi-functional carboxylic acid; e.g., d-alpha-tocopherol polyethylene glycol-1000 succinate), and macrogolglycerides (formed by alcoholysis of an oil and esterification of a polyalkylene glycol to produce a mixture of mono-, di- and tri-glycerides and mono- and di-esters; e.g., stearoyl macrogol-32 glycerides). Such pharmaceutical compositions are advantageously administered orally.

Pharmaceutical compositions of the present invention can comprise about 10% to about 50%, about 25% to about 50%, about 30% to about 45%, or about 30% to about 35% by weight of a metal salt of celecoxib; about 10% to about 50%, about 25% to about 50%, about 30% to about 45%, or about 30% to about 35% by weight of a an excipient which

inhibits crystallization; and about 5% to about 50%, about 10% to about 40%, about 15% to about 35%, or about 30% to about 35% by weight of a binding agent. In one example, the weight ratio of the metal salt of celecoxib to the excipient which inhibits crystallization to binding agent is about 1 to 1 to 1.

Solid dosage forms of the invention can be prepared by any suitable process, not limited to processes described herein.

An illustrative process comprises (a) a step of blending a celecoxib salt of the invention with one or more excipients to form a blend, and (b) a step of tableting or encapsulating the blend to form tablets or capsules, respectively.

In a preferred process, solid dosage forms are prepared by a process comprising (a) a step of blending a drug salt such as a celecoxib salt of the invention with one or more excipients to form a blend, (b) a step of granulating the blend to form a granulate, and (c) a step of tableting or encapsulating the blend to form tablets or capsules respectively. Step (b) can be accomplished by any dry or wet granulation technique known in the art, but is preferably a dry granulation step. A salt of the present invention is advantageously granulated to form particles of about 1 micrometer to about 100 micrometer, about 5 micrometer to about 50 micrometer, or about 10 micrometer to about 25 micrometer. One or more diluents, one or more disintegrants and one or more binding agents are preferably added, for example in the blending step, a wetting agent can optionally be added, for example in the granulating step, and one or more disintegrants are preferably added after granulating but before tableting or encapsulating. A lubricant is preferably added before tableting. Blending and granulating can be performed independently under low or high shear. A process is preferably selected that forms a granulate that is uniform in drug content, that readily disintegrates, that flows with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that is dense enough in bulk so that a batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

In an alternative embodiment, solid dosage forms are prepared by a process that includes a spray drying step, wherein a celecoxib salt is suspended with one or more excipients in one or more sprayable liquids, preferably a non-protic (e.g., non-aqueous or non-alcoholic) sprayable liquid, and then is rapidly spray dried over a current of warm air.

A granulate or spray dried powder resulting from any of the above illustrative processes can be compressed or molded to prepare tablets or encapsulated to prepare capsules. Conventional tableting and encapsulation techniques known in the art can be employed. Where coated tablets are desired, conventional coating techniques are suitable.

Excipients for tablet compositions of the invention are preferably selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less, in a standard disintegration assay.

Celecoxib dosage forms of the invention preferably comprise celecoxib in a daily dosage amount of about 10 mg to about 1000 mg, more preferably about 25 mg to about 400 mg, and most preferably about 50 mg to about 200 mg.

EXEMPLIFICATION

Example 1 (Comparative)

Celecoxib sodium salt from aqueous solution

To 77.3 mg of commercially-available celecoxib was added 1.0 mL distilled water, followed by 0.220 mL of 1 M NaOH (VWR). The mixture was heated with stirring to 60°C, whereupon an additional 1.0 mL distilled water was added. Solid NaOH (22 mg) was added, and the solid NaOH and celecoxib dissolved. The mixture was heated again

at 60°C to evaporate water. About 15 mL reagent-grade ethanol was added, while the mixture was stirred and heated at 60°C with air blowing over the solution. Heating continued until the solution was dry. The resulting material was analyzed by powder x-ray diffraction (PXRD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA), the results of which are seen in Figs. 1-3. The product was found to contain about 5.5 equivalents of water per equivalent of salt.

DSC analysis of the salt sample prepared above was performed using a Q1000 Differential Scanning Calorimeter (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (®2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (®2001 TA Instruments-Water LLC).

For the DSC analysis, the purge gas used was dry nitrogen, the reference material was an empty aluminum pan that was crimped, and the sample purge was 50 mL/minute.

DSC analysis of the sample was performed by placing 2.594 mg of sample in an aluminum pan with a crimped pan closure. The starting temperature was 20°C with a heating rate of 10°C/minute, and the ending temperature was 200°C. The resulting DSC analysis is shown in Fig. 1.

TGA analysis of the salt sample prepared above was performed using a Q500 Thermogravimetric Analyzer (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (®2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (®2001 TA Instruments-Water LLC).

For all of the TGA experiments, the purge gas used was dry nitrogen, the balance purge was 40 mL/minute N_2, and the sample purge was 60 mL/minute N_2.

TGA of the sample was performed by placing 2.460 mg of sample in a platinum pan. The starting temperature was 20°C with a heating rate of 10□C/minute, and the ending temperature was 300°C. The resulting TGA analysis is shown in Fig. 2.

A powder X-ray diffraction pattern for the salt sample prepared above was performed using a D/Max Rapid, Contact (Rigaku/MSC, The Woodlands, TX, U.S.A.), which uses as its control software RINT Rapid Control Software, Rigaku Rapid/XRD, version 1.0.0 ([8]1999 Rigaku Co.). In addition, the analysis software used were RINT Rapid display software, version 1.18 (Rigaku/MSC), and JADE XRD Pattern Processing, versions 5.0 and 6.0 ([8]1995-2002, Materials Data, Inc.).

For the PXRD analysis, the acquisition parameters were as follows: source was Cu with a K line at 1.5406Å; x-y stage was manual; collimator size was 0.3 mm; capillary tube (Charles Supper Company, Natick, MA, U.S.A.) was 0.3 mm ID; reflection mode was used; the power to the X-ray tube was 46 kV; the current to the X-ray tube was 40 mA; the omega-axis was oscillating in a range of 0-5 degrees at a speed of 1 degree/minute; the phi-axis was spinning at an angle of 360 degrees at a speed of 2 degrees/second; 0.3 mm collimator; the collection time was 60 minutes; the temperature was room temperature; and the heater was not used. The sample was presented to the X-ray source in a boron rich glass capillary.

In addition, the analysis parameters were as follows: the integration 2-theta range was 2-60 degrees; the integration chi range was 0-360 degrees; the number of chi segments was 1; the step size used was 0.02; the integration utility was cylint; normalization was used; dark counts were 8; omega offset was 180; and chi and phi offsets were 0.

The PXRD pattern for the compound prepared above is shown in Fig. 3. In the diffractogram of Fig. 3, the background has been removed.

Example 2 (Comparative)

Celecoxib-Lithium Salt Preparation Method: MO-116-49B

To 100mg of commercially available Celecoxib was added 0.35M LiOH(aq) (Lithium Hydroxide Monohydrate – Aldrich Cat#25,427-4, Lot 00331K1) solution with a Lithium:celecoxib ratio of 1.53:1 in a vial with a Teflon coated silicon rubber septum cap. The mixture was gently heated during dissolution with occasional swirling until all solids dissolved. Flowing dry nitrogen was blown over the solution for 2 days through stainless steel needles inserted into the septum cap until the solution was dry. Characterization of the product was achieved via DSC (Fig. 4), TGA (Fig. 5), Raman spectroscopy (Fig. 6) and PXRD (Fig. 7).

Unless specifically stated, all equipment and instrumentation used for analysis is the same as in Example 1.

Celecoxib-Lithium Salt Data (DSC)

1.56mg of collected sample was placed into an aluminum DSC pan with cover. The DSC pan was sealed with crimping and placed in TA Instruments Q1000 DSC. The sealed pan was heated 10°C/min to 300°C with 50ml/min nitrogen purge gas. Figure 4 is the resulting DSC analysis.

Celecoxib-Lithium Salt Data (TGA)

8.2290mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA. The pan was heated 10°C/min to 300°C with 40ml/min nitrogen purge gas. The results of the TGA are depicted in Fig. 5.

Celecoxib-Lithium Salt (MO-116-49A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the

Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collection scans. The parameters used for this analysis were:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec Number of exposures: 12 Number of background exposures: 6	Spectrometer: Visible Raman Microscope Laser: 785 nm Laser power level: 100% Laser polarization: Parallel Grating: 360 lines/mm Spectrograph aperture: 100 μm slit Sample position: Microscope Camera temperature: -50 C CCD rows binned: 89-150 CCD binning: On chip RIM position: Mirror Polarization analyzer: Out Illuminators: Of

The results of the Raman spectroscopy are depicited in Fig. 6.

Celecoxib-Lithium Salt Data (PXRD)

A small amount of collected sample was placed in a 0.3mm glass PXRD tube.. The tube was placed into a Rigaku D/Max Rapid PXRD and set to: Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes.

Example 3 (Comparative)

Celecoxib-Potassium Salt: Preparation Method MO-116-49A

100mg of Celecoxib (Fako Ilaclari A,S,) was dissolved in a 0.35M KOH(aq) solution (Potassium Hydroxide – Spectrum, Cat# P0180, Lot#PN0690) with a Potassium:Celecoxib ratio of 1.40:1 in a vial with a Teflon coated silicon rubber septum cap. The resulting solution was gently warmed during dissolution with occasional swirling until all solids dissolved. After all solids were dissolved, the solution was dried

by flowing dry nitrogen over the solution for 2 days through stainless steel needles inserted into the septum cap. Analysis of the resulting product was performed. Characterization of the product was achieved via DSC (Fig. 8,) TGA (Fig. 9), Raman spectroscopy (Fig. 10) and PXRD (Fig. 11).

Celecoxib-Potassium Salt (MO-116-49A) Data (DSC)

1.119 mg of collected sample was placed into an aluminum DSC pan with cover. The pan was sealed with crimping and placed into a TA Instruments Q1000 DSC. The DSC was heated 10°C/min to 300°C with 50ml/min nitrogen purge gas. The results are depicted in the graph of Fig. 8.

Celecoxib-Potassium Salt (MO-116-49A) Data (TGA)

5.9890 mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA and heated10°C/min to 90°C, held for 10 minutes, ramped 10°C/min to 300°C, and held for 10 minutes with 40ml/min nitrogen purge gas. The results are depicted in Fig. 9.

Celecoxib-Potassium Salt (MO-116-49A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collections. The parameters used for this analysis were:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec Number of exposures: 12 Number of background exposures: 6	Spectrometer: Visible Raman Microscope Laser: 785 nm Laser power level: 100% Laser polarization: Parallel Grating: 360 lines/mm Spectrograph aperture: 100 μm slit Sample position: Microscope Camera temperature: -50 C CCD rows binned: 89-150 CCD binning: On chip RIM position: Mirror Polarization analyzer: Out Illuminators: Of

The results are depicted in Fig. 10.

Celecoxib-Potassium Salt (MO-116-49A) Data (PXRD)

A small amount of collected sample was placed in a 0.3mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes. The results are depicted in Fig. 11.

Example 4

A propylene glycol solvates of the sodium salt of celecoxib was prepared. To a solution of celecoxib (312 mg; 0.818 mmol) in Et_2O (6 mL) was added propylene glycol (0.127 ml, 1.73 mmol). To the clear solution was added NaOEt in EtOH (21%, 0.275 L,0.817 mmol). After 1 minute, crystals began to form. After 5 minutes, the solid had completely crystallized. The solid was collected by filtration and was washed with Et_2O (10 mL). The off-white solid was then air-dried and collected. This was a 1:1 solvate. The solid was characterized by TGA and PXRD. The results are depicted in Fig. 12 and 13.

Example 5

A propylene glycol solvate of the potassium salt of celecoxib was prepared. To a solution of celecoxib (253 mg, 0.664 mmol) in Et_2O (6 mL) was added propylene glycol (0.075 ml, 1.02 mmol). To the clear solution was added KO*t*Bu in THF (1 M, 0.66 mL, 0.66 mmol). Crystals immediately began to form. After 5 minutes, the solid had completely crystallized. The solid was collected by filtration and was washed with Et_2O (10 mL). The white solid was then air-dried and collected. This solid was a 1:1 solvate. The solid was characterized by TGA and PXRD. The results are depicted in Fig. 14 and 15.

Example 6

A propylene glycol solvate of lithium salt of celecoxib was prepared. To a solution of celecoxib (264 mg, 0.693 mmol) in Et_2O (8 mL) was added propylene glycol (0.075 ml, 1.02 mmol). To the clear solution was added *t*Bu-Li in pentane (1.7 M, 0.40 mL, 0.68 mmol). A brown solid formed immediately but dissolved within one minute yielding white solid. The white solid crystallized completely after 10 minutes. The solid was collected by filtration and was washed with Et_2O (10 mL). The white solid was then air-dried and collected. The solid was a 1:1 solvate. The solid was characterized by TGA and the results are depicted in Fig. 16.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

Example 7

A propylene glycol solvate of a sodium salt of Naproxen was prepared. To a solution of Naproxen (mg, mmol) in Et_2O (10 mL) was added propylene glycol (ml, mmol). To the clear solution was added NaOEt in EtOH (21%, mL, mmol). The solution became slightly yellow due to NaOEt. After 1 minute, crystals begin to form. After 5 minutes, the solid had completely crystallized. The solid was collected by filtration and was

washed with Et_2O (10 mL). The product was then air-dried and collected. The solvate was 2:1 Naproxen Na:PG. The solid was characterised by TGA and PXRD. The results are depicted in Fig. 17 and Fig. 18.

CLAIMS:

1. A pharmaceutical composition comprising a propylene glycol solvate of a drug which is hygroscopic or which has low aqueous solubility.

2. A composition according to claim 1, wherein the mole ratio of propylene glycol to drug in the solvate is in the range 0.25 to 2.

3. A composition according to claim 1; wherein the solvate is in a crystalline form.

4. A composition according to claim 3, having a powder X-ray diffraction spectrum which differs from the corresponding powder X-ray diffraction spectrum of the unsolvated drug by at least one property selected from

(i) a loss of at least one peak;

(ii) shifting of more than half the peaks at the 2-theta angle by at least 0.3°; and

(iii) formation of at least one new peak.

5. A composition according to claim 1, wherein the solvate is stable to temperatures of up to 50°C under a stream of gas in a thermogravimetric analysis apparatus.

6. A composition according to claim 1, wherein the drug is in the form of a metal salt.

7. A composition according to claim 6, wherein the metal is an alkali metal or an alkaline earth metal.

8. A composition according to claim 7, wherein the metal is selected from Na, K, Li, Ca and Mg.

9. A composition according to claim 1, wherein the drug is selected from the group of hygroscopic drugs consisting of Celecoxib, Naproxen, Methyl prednisolone succinate ester, Impinem/Cilastatin, Fomivirsen sodium, Cerivastatin sodium, Dalfopristin/Quinopristin, Gonadorelin HC1(decapeptide), Clindamycin phosphate (ester prodrug), Famciclovir, Cyanocobalamin, Tolcapone, Epirubicin HC1, Colestipol HC1 (anion exc.), Penicillin G potassium, Bacitracin (peptide), Fluvastatin sodium, Diclofenac sodium, Pilocarpine HC1, Bethanechol chloride, Trientine 2 (CH1), Montelukast sodium, Mechlorethamine HC1, Hydrocortisone phosphate ester, Dexamethasone phosphate ester, Chromolyn sodium, Pyridostigmine bromide, Phentermine HC1, Telmisartan, Daunorubicin HC1, Praziquantel, and Pentosan polysulfate sodium.

10. A composition according to claim 1, wherein the drug has low aqueous solubility and is selected from the group consisting of steroid drugs.

11. A composition according to claim 1, which further comprises a pharmaceutically-acceptable diluent, excipient or carrier.

12. A propylene glycol solvate of a sodium salt of celecoxib, which has peaks at 2-theta angles of approximately 3.8°, 7.6°, 8.2°, 11.3° and 20.6°, in a powder X-ray diffraction spectrum.

13. A propylene glycol solvate of a potassium salt of celecoxib, which has peaks at 2-theta angles of approximately 3.8°, 7.5°, 11.3° and 18.3°, in a powder X-ray diffraction spectrum.

14. A propylene glycol solvate of a sodium salt of naproxen, which has peaks at 2-theta angles of approximately 6.7°, 9.7°, 15.8°, 18.6°, 20.8° and 22.8°, in a powder X-ray diffraction spectrum.

15. A method for preparing a propylene glycol solvate of a drug, which method comprises:

(a) contacting propylene glycol with a hygroscopic drug in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) collecting the solvate, wherein the drug is hygroscopic or has low aqueous solubility.

16. A method according to claim 15, wherein the step of crystallizing the solvate comprises changing the pH of the solution to precipitate the solvate.

17. A method according to claim 16, wherein the pH is raised to render the solution alkaline.

18. A method according to claim 15, wherein the step of collecting the solvate includes separating the solution phase from the solvate.

19. A method according to claim 18, wherein crystalline solvate is dried to remove excess solution phase.

20. A method for decreasing the hygroscopicity of a drug, which method comprises

(a) contacting the drug with propylene glycol in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) collecting the solvate, wherein the solvate has decreased hygroscopicity as compared to the drug.

21. A method for increasing the aqueous solubility of a drug, which method comprises

(a) contacting the drug with propylene glycol in solution;

(b) crystallizing a propylene glycol solvate of the drug from the solution; and

(c) collecting the solvate, wherein the solvate has increased aqueous solubility as compared to the drug.

22. A method according to claim 15, wherein the solvate has a powder X-ray diffraction spectrum which differs from the corresponding powder X-ray diffraction spectrum of the unsolvated drug by at least one property selected from

(i) a loss of at least one peak;

(ii) shifting of more than half the peaks at the 2-theta angle by at least 0.3°; and

(iii) formation of at least one new peak.

23. A method according to claim 15, wherein the solvate is stable to temperatures of up to 50°C under a stream of gas in a thermogravimetric analysis apparatus.

24. A method according to claim 15, wherein the drug is in the form of a metal salt.

25. A method according to claim 24, wherein the metal is an alkali metal or an alkaline earth metal.

26. A method according to claim 25, wherein the metal is selected from Na, K, Li, Ca and Mg.

27. A method according to claim 1, wherein the drug comprises . Celecoxib, Naproxen, Methyl prednisolone succinate ester, Impinem/Cilastatin, Fomivirsen sodium, Cerivastatin sodium, Dalfopristin/Quinopristin, Gonadorelin HC1(decapeptide), Clindamycin phosphate (ester prodrug), Famciclovir, Cyanocobalamin, Tolcapone, Epirubicin HC1, Colestipol HC1 (anion exc.), Penicillin G potassium, Bacitracin (peptide), Fluvastatin sodium, Diclofenac sodium, Pilocarpine HC1, Bethanechol chloride, Trientine 2 (CH1), Montelukast sodium, Mechlorethamine HC1, Hydrocortisone phosphate ester, Dexamethasone phosphate ester, Chromolyn sodium,

Pyridostigmine bromide, Phentermine HC1, Telmisartan, Daunorubicin HC1, Praziquantel, and Pentosan polysulfate sodium.

28. A method according to claim 1, wherein the drug comprises has low aqueous solubility and is selected from the group consisting of steroid drugs.

Abstract

Pharmaceutical Compositions

A pharmaceutical composition comprising a propylene glycol solvate of a drug which is hygroscopic or which has low aqueous solubility.

FIG. 1

DSC
File: G:\Data\DSC\malty\Pl336\dsc_67_2b_12.0
Operator: MLP
Run Date: 21-Mar-02 16:24
Sample: dsc_67_2b_12
Size: 2.6940 mg
Method: Ramp
Comment: TPL336Na
100.79°C
76.02°C
60.62°C
Heat Flow (W/g)
Temperature (°C)
Universal V4.2E Instruments

FIG. 2

TGA
File: G:\Data\TGA\data\TP1356.tad 57_26_13.tr
Operator: MLP
Run Date: 21-Mar-03 16:20
Sample: mg 57_26_13
Size: 2.4060 mg
Method: Hi-Res - Dynamic
Comment: TP1356Na
100
95
90
85
80
75
(%) ɯɐɓ
32.76°C
19.23%
(0.3264mg)
39.83°C
70.22°C
2.739%
(0.0873mg)
70.66°C
147.60°C
1.809%
(0.1035mg)
159.33°C
0
50
100
150
200
250
Temperature (°C)

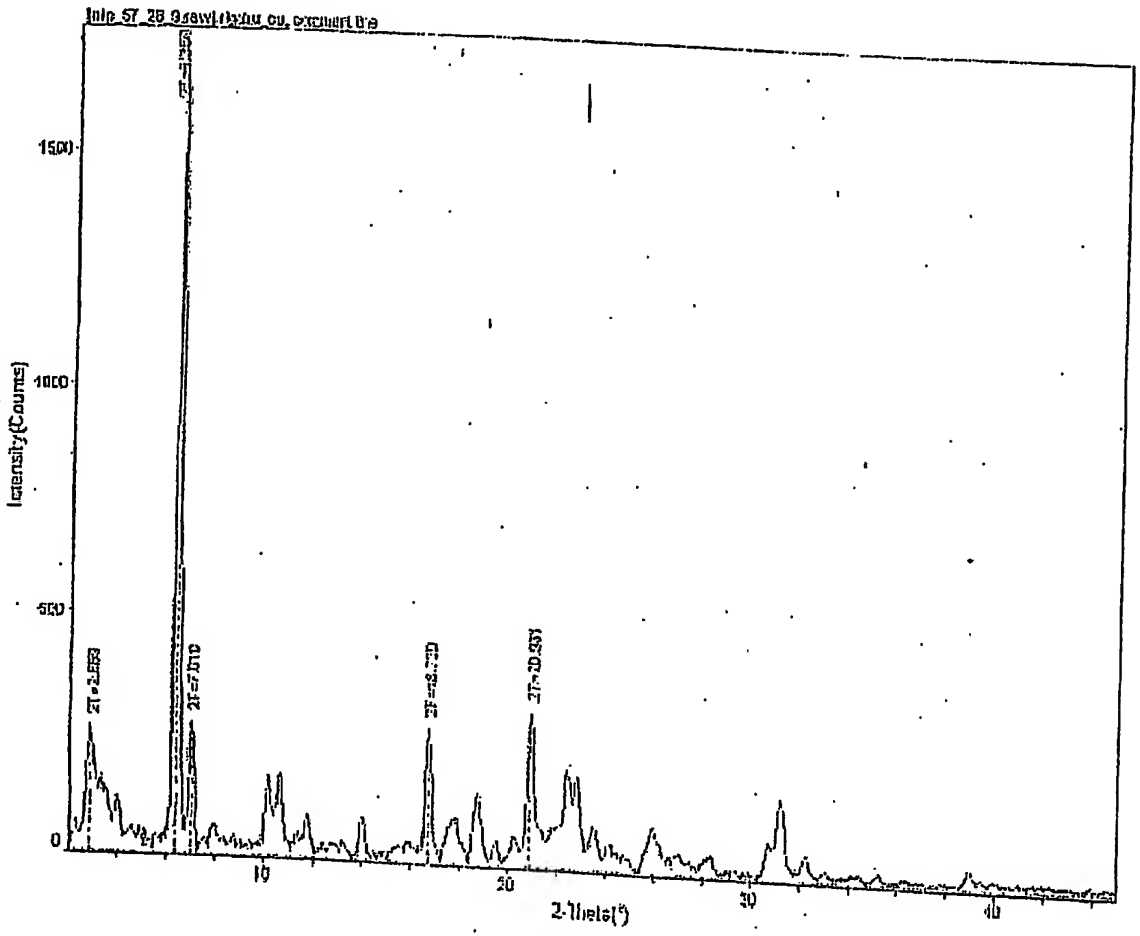


FIG. 3

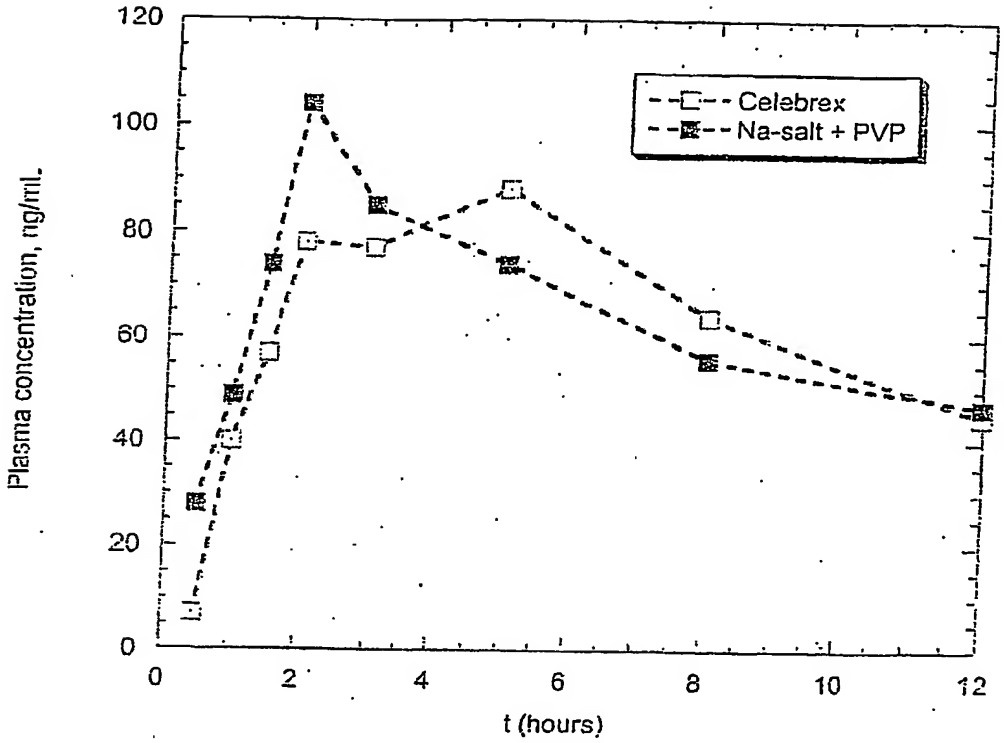

120
100
80
60
40
20
0
0
2
4
6
8
10
12
Plasma concentration, ng/mL
t (hours)
Celebrex
Na-salt + PVP

FIG. 4A

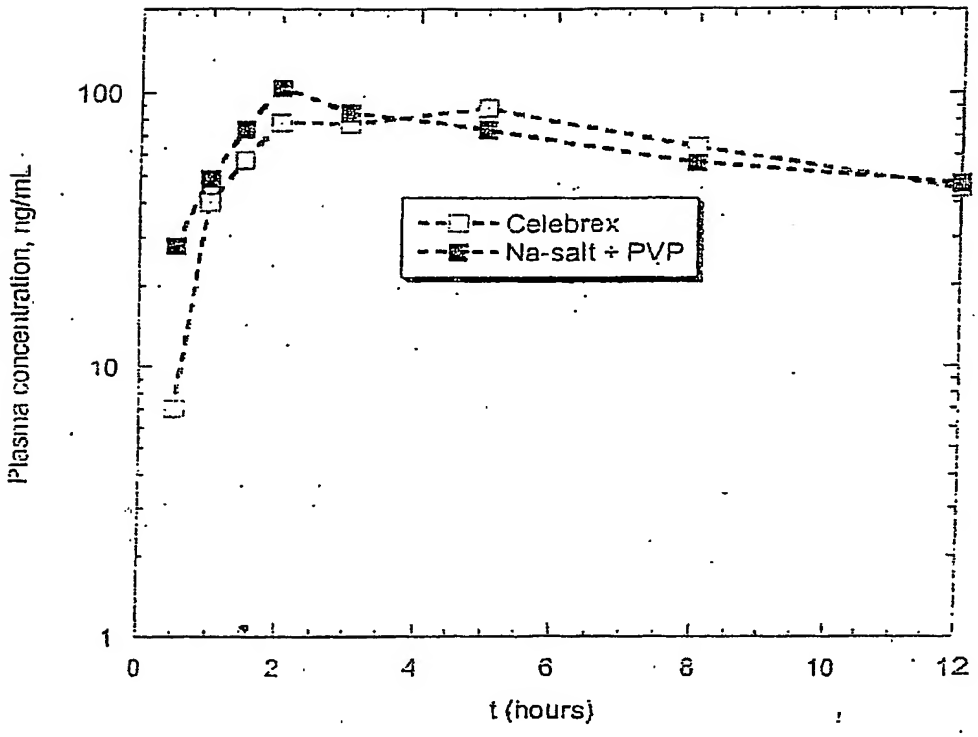

100
10
1
Plasma concentration, ng/mL
0
2
4
6
8
10
12
t (hours)
Celebrex
Na-salt + PVP

FIG. 4B

	Formulation	Dose Level (mg/kg)	C_{max} (ng/mL)	T_{max} (min)	$AUC_{(0-\infty)}$ (ng·hr/mL)	$T_{1/2}$ (hr)	Volume of Distribution at Steady State (mL/kg)	Clearance Rate (mL/hr-kg)	Bioavailability (%)
Mean	Celecoxib IV	1	718	NA	3808	8.21	2498	278	NA
SD		NA	91	NA	933	2.85	590	77	NA
Mean	Celecoxib PO	5.09	654	1.25	7663	9.3	NA	798	40.05
SD		0.050	199	0.88	3119	3.48	NA	317	15.45
Mean	Celecoxib Sodium PO	5.05	2142	0.75	16426	9.0	NA	323	85.80
SD		0.121	569	0.27	4150	2.71	NA	77	7.82

FIG. 5

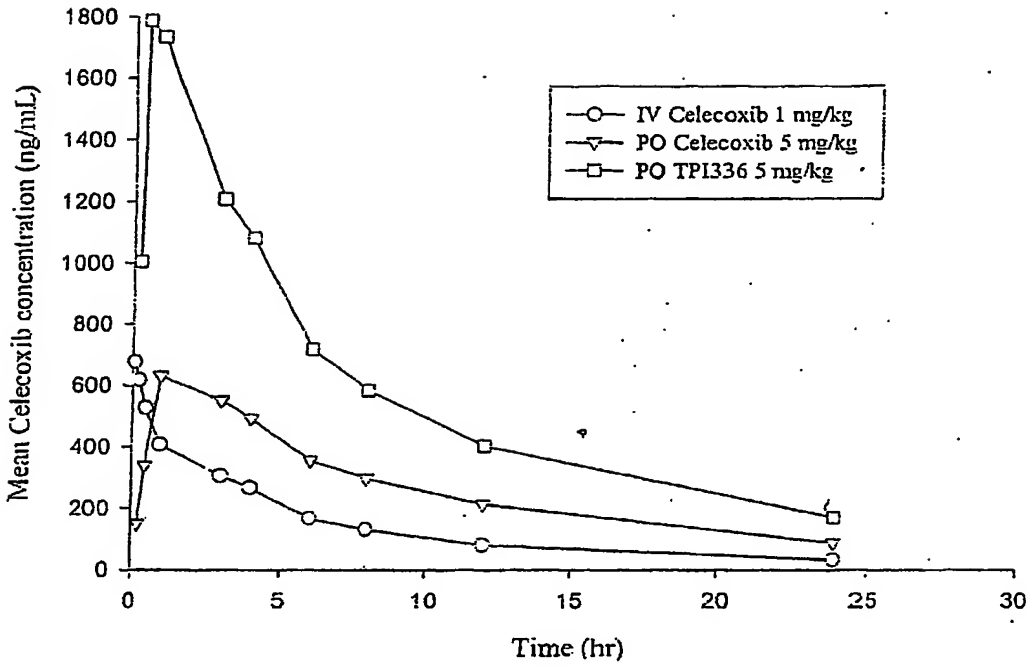
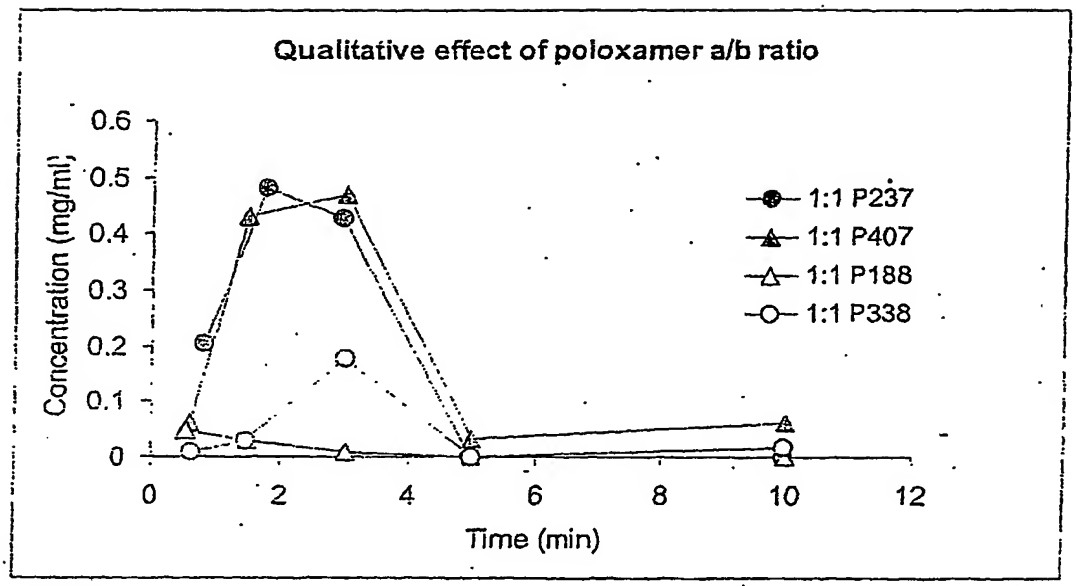

1800
1600
1400
1200
1000
800
600
400
200
0
Mean Celecoxib concentration (ng/mL)
0
5
10
15
20
25
30
Time (hr)
IV Celecoxib 1 mg/kg
PO Celecoxib 5 mg/kg
PO TPI336 5 mg/kg

FIG. 6

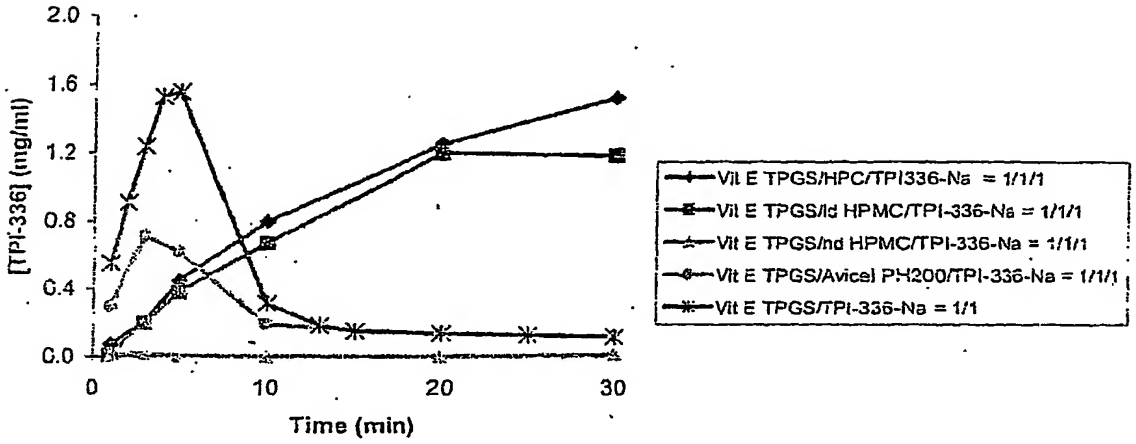


Poloxamer	Physical form	a	b	Average molecular weight	Percent a	Percent b	Ratio a/b
124	Liquid	12	20	2090-2360	0.38	0.63	0.60
188	Solid	80	27	7680-9510	0.75	0.25	2.96
237	Solid	64	37	6840-8830	0.63	0.37	1.73
338	Solid	141	44	12 700-17 400	0.76	0.24	3.20
407	Solid	101	56	9840-14 600	0.64	0.36	1.80

$HO(C_2H_4O)_a(C_3H_5O)_b(C_2H_4O)_aH$

FIG. 7

Effects of Celluloses on Dissolution of 1/1 Vitamin E TPGS/TPI-336-Na at Room Temperature



hd HPMC = High density
ld HPMC = low density

FIG. 8

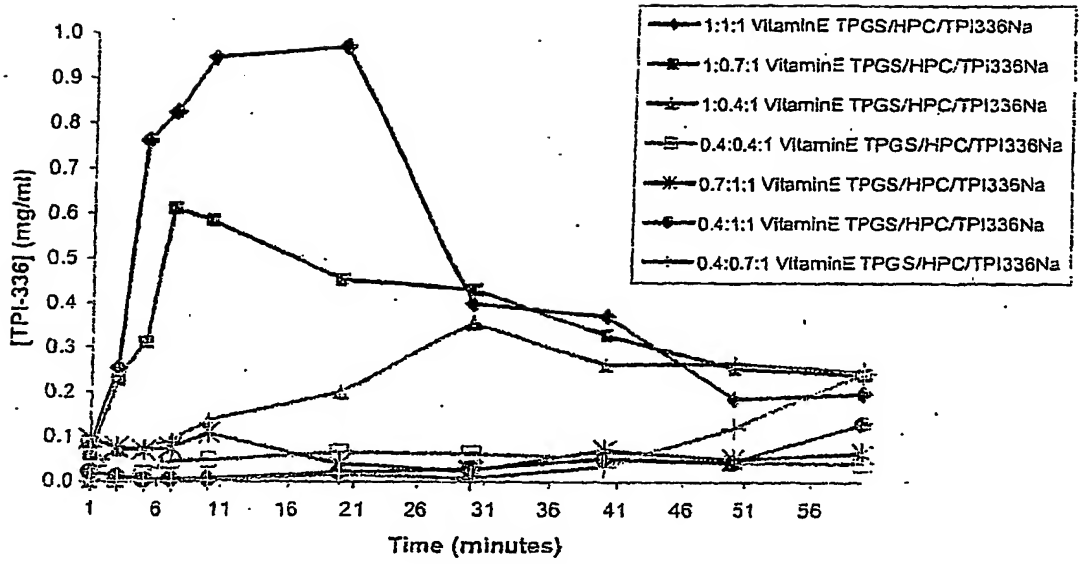

1:1:1 VitaminE TPGS/HPC/TPI336Na
1:0.7:1 VitaminE TPGS/HPC/TPI336Na
1:0.4:1 VitaminE TPGS/HPC/TPI336Na
0.4:0.4:1 VitaminE TPGS/HPC/TPI336Na
0.7:1:1 VitaminE TPGS/HPC/TPI336Na
0.4:1:1 VitaminE TPGS/HPC/TPI336Na
0.4:0.7:1 VitaminE TPGS/HPC/TPI336Na
[TPI-336] (mg/ml)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
1
6
11
16
21
26
31
36
41
46
51
56
Time (minutes)

FIG. 9

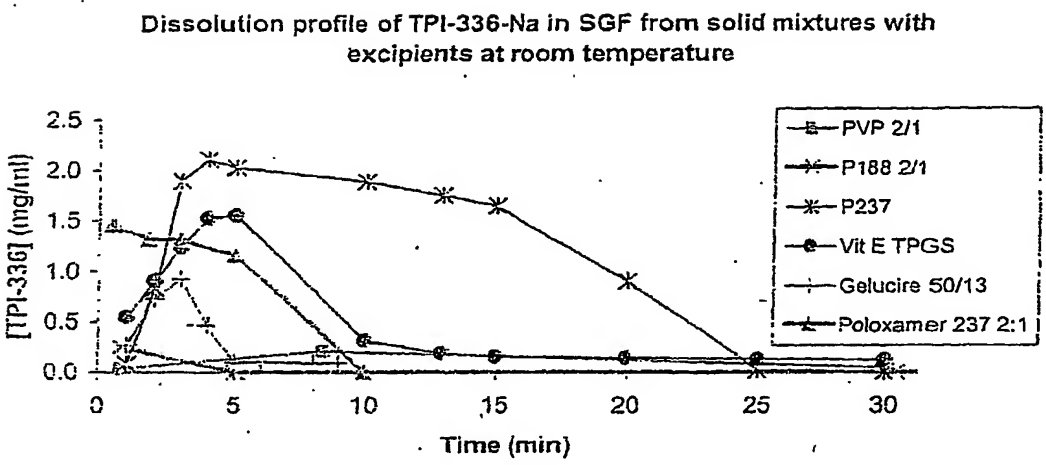

Dissolution profile of TPI-336-Na in SGF from solid mixtures with excipients at room temperature
[TPI-336] (mg/ml)
2.5
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
25
30
Time (min)
PVP 2/1
P188 2/1
P237
Vit E TPGS
Gelucire 50/13
Poloxamer 237 2:1

FIG. 10

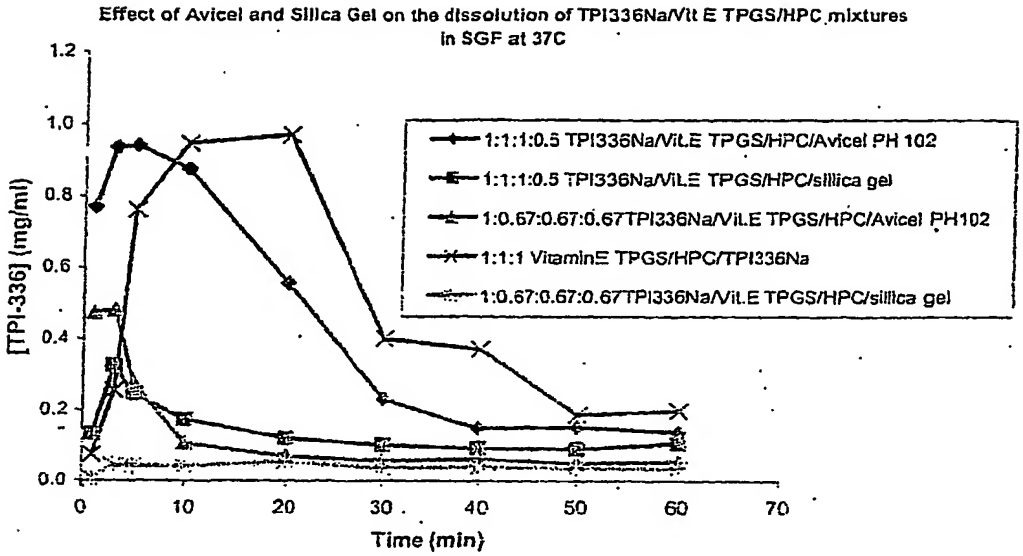

Effect of Avicel and Silica Gel on the dissolution of TPI336Na/Vit E TPGS/HPC mixtures in SGF at 37C
[TPI-336] (mg/ml)
Time (min)
1:1:1:0.5 TPI336Na/VitE TPGS/HPC/Avicel PH 102
1:1:1:0.5 TPI336Na/VitE TPGS/HPC/sillica gel
1:0.67:0.67:0.67TPI336Na/VitE TPGS/HPC/Avicel PH102
1:1:1 VitaminE TPGS/HPC/TPI336Na
1:0.67:0.67:0.67TPI336Na/Vit.E TPGS/HPC/silica gel

FIG. 11

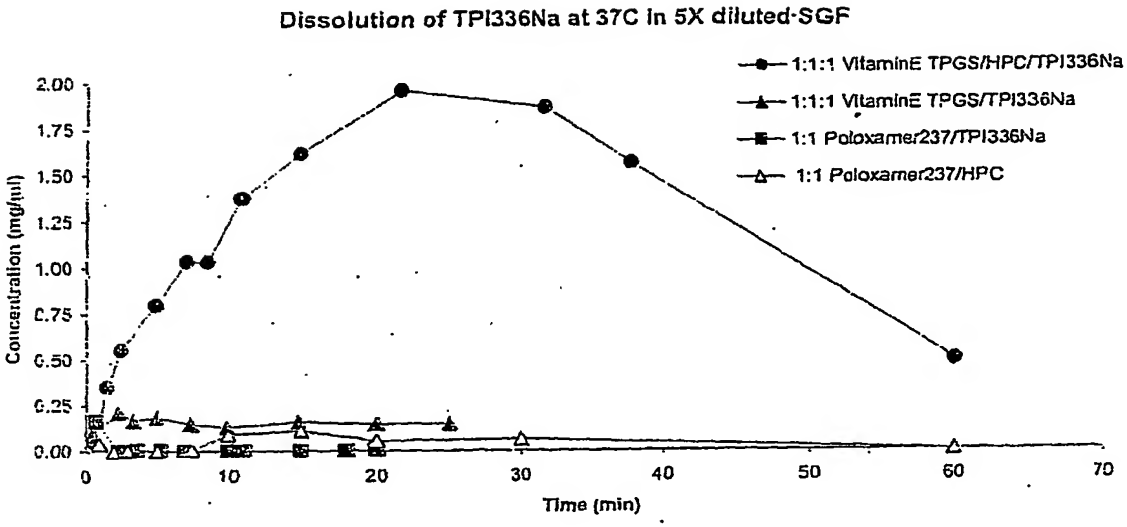

Dissolution of TPI336Na at 37C in 5X diluted-SGF
1:1:1 VitaminE TPGS/HPC/TPI336Na
1:1:1 VitaminE TPGS/TPI336Na
1:1 Poloxamer237/TPI336Na
1:1 Poloxamer237/HPC
Concentration (mg/ml)
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
50
60
70
Time (min)

FIG. 12

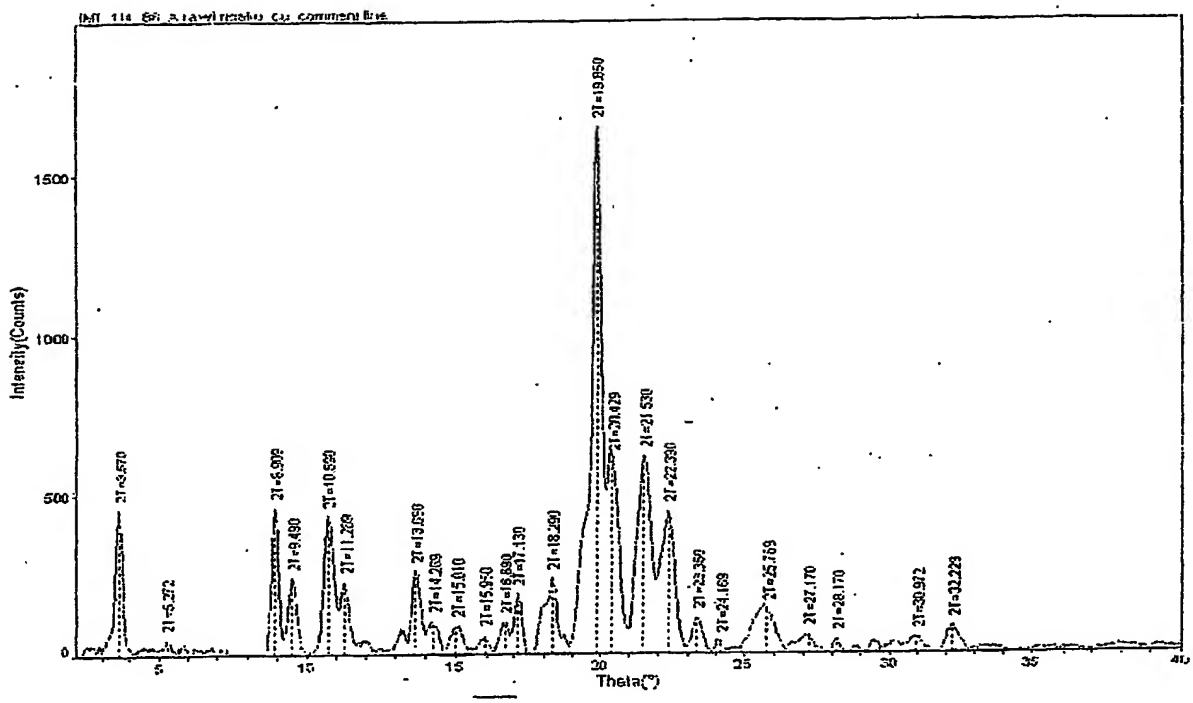

Intensity(Counts)
1500
1000
500
0
Theta(°)
2T=19.650
2T=21.530
2T=22.390
2T=6.570
2T=6.902
2T=9.490
2T=10.699
2T=11.269
2T=13.059
2T=14.269
2T=15.010
2T=15.950
2T=16.880
2T=17.130
2T=18.290
2T=20.029
2T=23.359
2T=24.169
2T=25.769
2T=27.170
2T=28.170
2T=30.972
2T=32.229

FIG. 13A

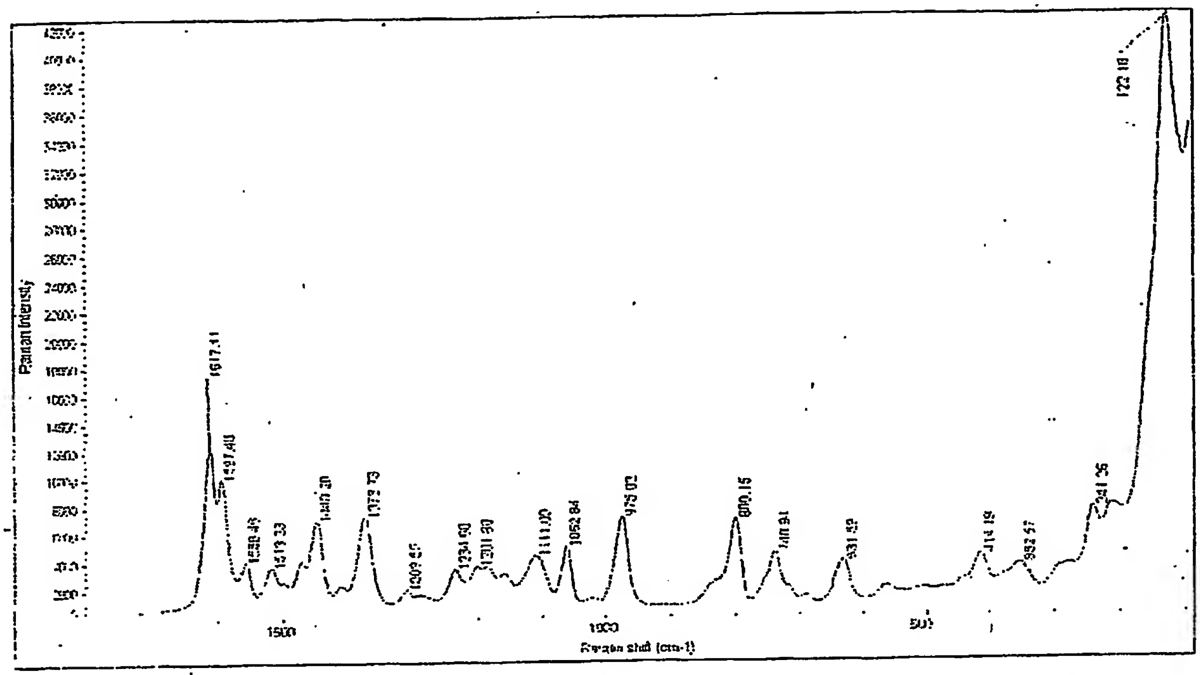

Raman Intensity
1617.11
1052.84
122.18
1500
1000
500
Raman shift (cm-1)

FIG. 13B

FIG. 14

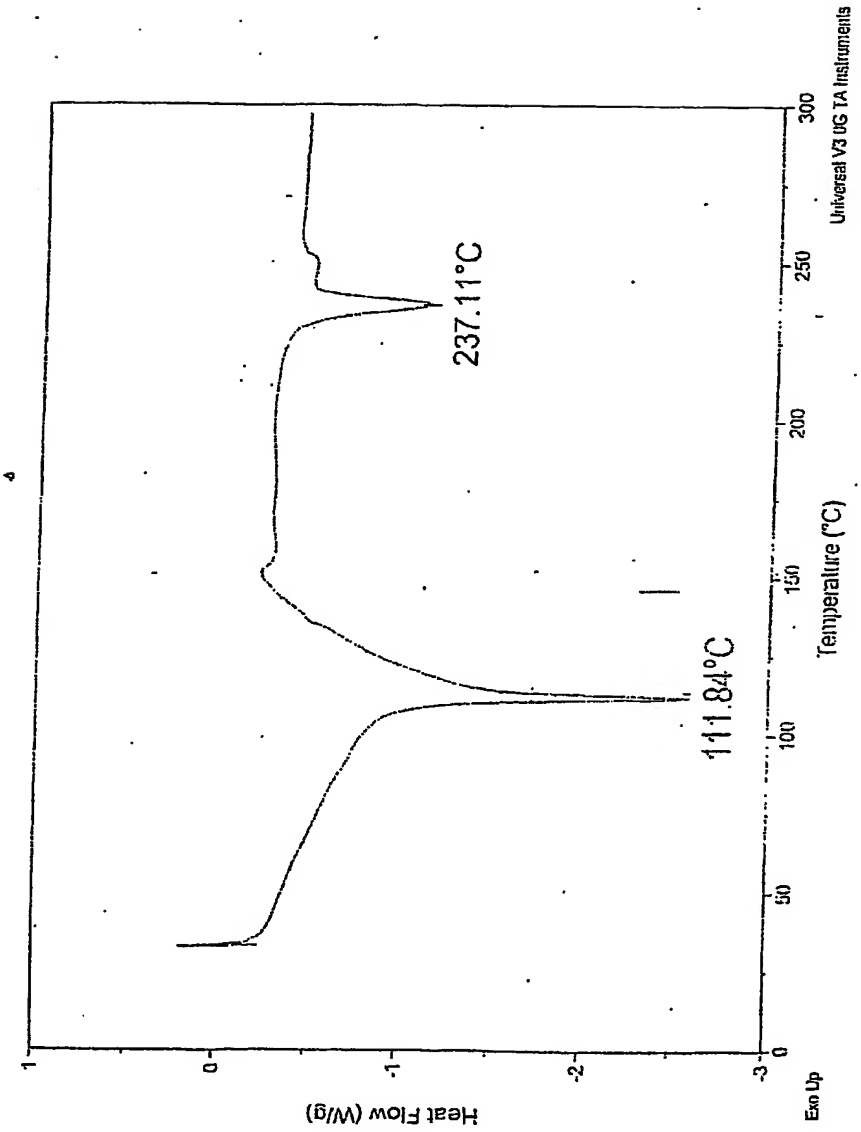

237.11°C
111.84°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
Universal V3.0G TA Instruments

FIG. 15

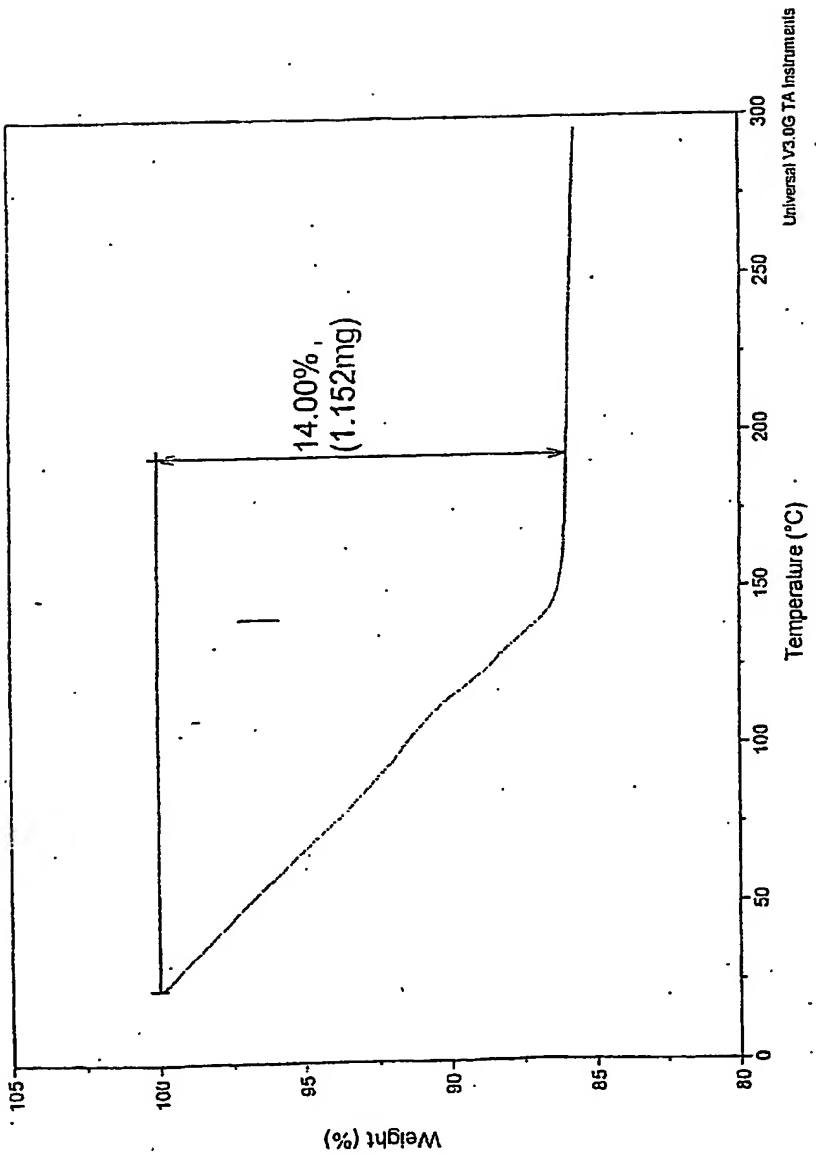

14.00%,
(1.152mg)
Weight (%)
105
100
95
90
85
80
0
50
100
150
200
250
300
Temperature (°C)
Universal V3.0G TA Instruments

FIG. 16

130.37
211.43
241.70
351.98
415.72
562.53
633.94
740.91
800.67
976.50
1062.85
1115.24
1159.79
1202.02
1233.29
1309.47
1374.03
1449.56
1518.98
1558.98
1596.93
1617.10
Inv-116-488_celecoxib-LJ
Raman shift (cm-1)
Int

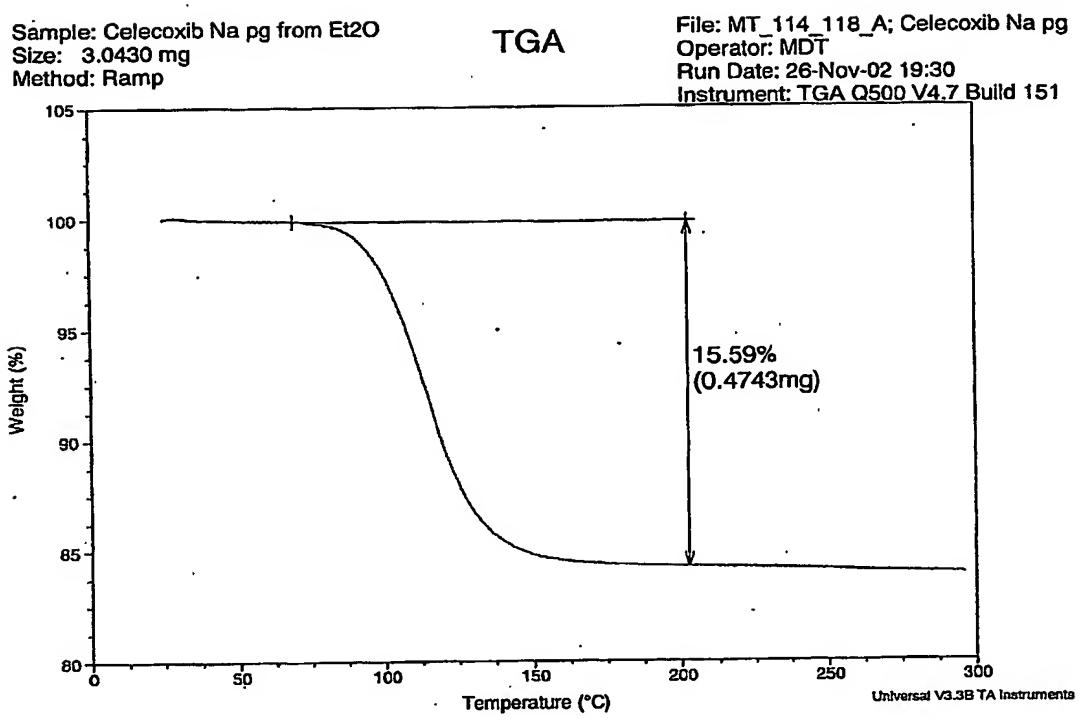

Sample: Celecoxib Na pg from Et2O
Size: 3.0430 mg
Method: Ramp
TGA
File: MT_114_118_A; Celecoxib Na pg
Operator: MDT
Run Date: 26-Nov-02 19:30
Instrument: TGA Q500 V4.7 Build 151
105
100
95
90
85
80
Weight (%)
15.59%
(0.4743mg)
0
50
100
150
200
250
300
Temperature (°C)
Universal V3.3B TA Instruments

Fig. 17

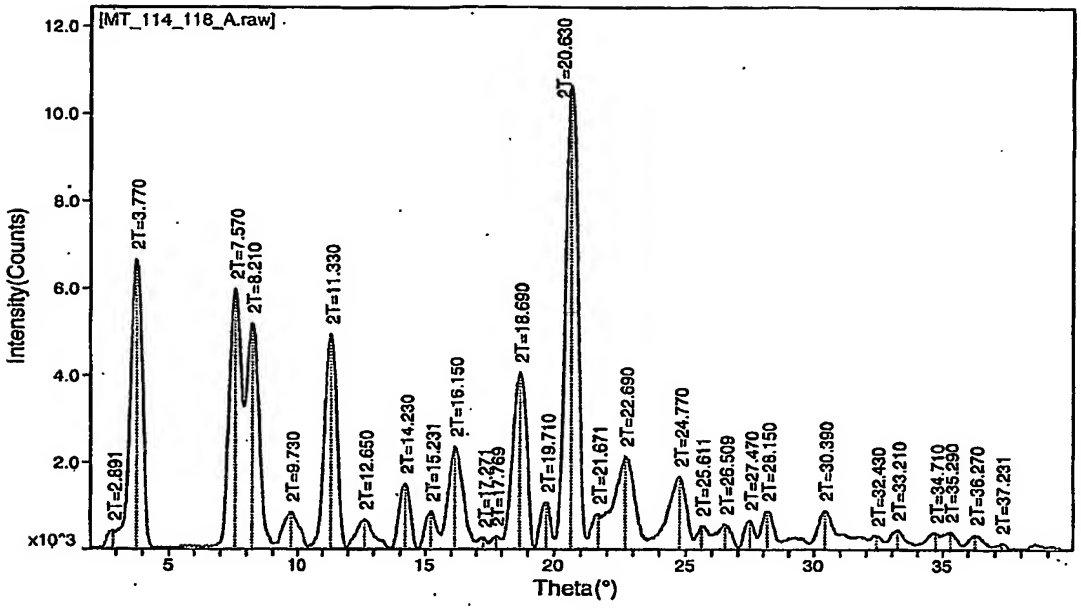

[MT_114_118_A.raw]
Intensity(Counts)
x10^3
Theta(°)
2T=2.891
2T=3.770
2T=7.570
2T=8.210
2T=9.730
2T=11.330
2T=12.650
2T=14.230
2T=15.231
2T=16.150
2T=17.271
2T=17.769
2T=18.690
2T=19.710
2T=20.630
2T=21.671
2T=22.690
2T=24.770
2T=25.611
2T=26.509
2T=27.470
2T=28.150
2T=30.390
2T=32.430
2T=33.210
2T=34.710
2T=35.290
2T=36.270
2T=37.231

Fig. 18

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